SM

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/866,866	05/29/2001	Brian Sorrentino	1340-1-021CIP2	4688

31949 7590 04/08/2004

LICATA & TYRRELL P.C.
66 E. MAIN STREET
MARLTON, NJ 08053

EXAMINER	
LI, QIAN JANICE	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 04/08/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/866,866	SORRENTINO ET AL.	
	Examiner	Art Unit	
	Q. Janice Li	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 January 2004* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16,17 and 21-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16,17 and 21-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 May 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/20/04 has been entered.

The Declaration of Dr. Balzas Sarkadi filed 10/20/03 has been considered. No claim is amended. Claims 16, 17, and 21-28 are pending and under current examination.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the new grounds of rejections will not be reiterated. The statement in the Declaration would be addressed to the extent that they apply to current rejection.

Claim Objections

Claim 16 is objected to because the term "BCRP" should be spell out the first time it appears in the claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 16, 17, 21-28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The methodology for determining adequacy of Written Description to convey that applicant was in possession of the claimed invention includes determining whether the application describes an actual reduction to practice, determining whether the invention is complete as evidenced by drawings, or determining whether the invention has been set forth in terms of distinguishing identifying characteristics as evidenced by other descriptions of the invention that are sufficiently detailed to show that applicant was in possession of the claimed invention (*Guidelines for Examination of Patent Applications under 35 U.S.C. § 112, p 1 "Written Description" Requirement;* Federal Register/ Vol 66. No. 4, Friday, January 5, 2001; II Methodology for Determining Adequacy of Written Description (3.)).

The claims are directed to an isolated antibody that recognizes an extracelluar portion of a BCRP, and wherein the extracelluar portion of the BCRP is in its natural conformation. Given the broadest reasonable interpretation, the claims embrace a genus of antibodies encompassing a large number of antibodies recognizing different epitopes of the extracelluar portion of the BCRP in its natural conformation, wherein for

each epitope, the antibodies could be monoclonal, polyclonal, chimeric or humanized. However, the specification fails to provide an adequate disclosure for the genus of the claimed invention in terms of distinguishing characteristics of the genus.

The specification teaches that the antibody could be made with an external epitope of BCRP using various procedures known in the art, the section spanning pages 20-26 discussing the production of such antibody citing numerous prior art publications and patents. However, the specification fails to disclose even one such antibody by its sequence structure, let alone a core structure of the claimed genus that would allow the skilled artisan to determine whether a particular antibody belongs to the claimed genus, and the specification fails to teach how to determine whether an antibody recognizes the extracellular portion of the BCRP in its natural conformation. Therefore, the specification fails to provide an adequate description to teach the structures, and the identifying characteristics of the genus of antibodies encompassed by the claims and the specification fails to teach the structure-function relationship with respect to antibodies that only recognize the external epitope of a BCRP that is in its natural conformation, and accordingly does not provide a reasonable guide for those seeking to practice the invention.

An adequate written description for an antibody requires more than a mere statement that it is part of the invention; what is required is a description of the chemical structures and physical properties of the antibody itself. It is not sufficient to define the antibody solely by its principal biological property, i.e. "recognizes an extracellular portion of a BCRP in its natural conformation", because disclosure of no more than that,

as in the instant case, is simply a wish to know the identity of any antibody with that biological property. Also, naming a type of material generically known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. Thus, claiming all antibodies that achieve a result without defining what means will do is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). The court has made it very clear "CONCEPTION OF CHEMICAL COMPOUND REQUIRES THAT INVENTOR BE ABLE TO DEFINE COMPOUND SO AS TO DISTINGUISH IT FROM OTHER MATERIALS, AND TO DESCRIBE HOW TO OBTAIN IT, RATHER THAN SIMPLY DEFINING IT SOLELY BY ITS PRINCIPAL BIOLOGICAL ACTIVITY". *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). In the instant case, the only BCRP antibody that was contemplated in the specification appears to be a monoclonal antibody produced by immunizing mice with BCRP transfected 3T3 cells, and selecting for hybridoma clones (Specification, page 39). However, the specification fails to teach the structure of the antibody and the specification as written does not made clear whether such antibody was indeed obtained. Even if applicants could provide evidence that the recited antibody has been in possession of the applicants at the time of the effective filing date, the antibody discussed has not satisfied the written description requirement for the claimed genus because as indicated in the following case law, one cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to

mammalian FGF's were found to be unpatentable due to lack of written description for that broad class, because the specification provided only the bovine sequence.

In view of these considerations, a skilled artisan would not have viewed the teachings of the specification as sufficient to show that the applicant was in possession of the claimed invention commensurate to its scope because it does not provide adequate written description for the broad class of antibodies having the recited characteristics.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 16, 17, 21-28 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention (see *In re Wands*, 858 F. 2d 731, 737, 8 USPQ 2d 1400, 1404, 1988). These factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction provided.

These claims are drawn to any isolated antibody that recognizes an extracellular portion of a BCRP in its natural conformation, however, as indicated *supra* in the written description section, the specification fails to provide an adequate description for a single antibody with the claimed property or for the broad class of antibodies encompassed by the claims, and the specification fails to teach how to determine whether an extracellular epitope recognized by an antibody is in its natural conformation, thus it fails to support the full scope of the claims.

It is noted in the Declaration of Dr. Balzas Sarkadi submitted by the applicants, Dr. Sarkadi indicated that as of the priority date of this application, there was no method known in the art to reliably produce an isolated antibody that recognizes an extracellular portion of the ABC transporter BCRP in a living cell, and one of skill in this field would not have expected that conventional methods available for generating antibodies as of the instant effective filing date could be used to generating the claimed antibody. According to such statement, it is unpredictable to make the claimed antibody, and the specification fails to provide an enabling disclosure for what is now claimed because the only method for preparing the claimed antibody in the specification is taught by referring to various prior art of record, such as Kohler et al, Cote et al, Morrison et al, and USP 5,476,786 (Specification, page 21, lines 8-32) or methods known in the art (Specification, page 39) as taught by *Mechetner et al* (US 5,994,088). As such, one cannot extrapolate the teachings of the specification to the scope of the claims because the skilled artisan cannot envision the detailed structures of antibodies encompassed by these claims, or how to make the invention without first carrying out undue

experimentation to determine which of the antibodies would have the recited function and how to reliably producing such. Accordingly, if the prior art fails to teach a method of making such antibodies, so does the specification.

Moreover, the specification fails to teach that the antibody obtained by the applicants indeed recognizes an extracellular epitope in its natural conformation because proving such, an X-ray crystallography showing the three-dimensional structure of the epitope relative to the antibody may be necessary, yet the specification is silent with this respect. The specification only teaches that clones that can *detect* expression of the HaBCRP vector in bone marrow cells are expanded for large-scale preparation. Here, the selection of antibodies is not according to the structural feature but a functional one, i.e. capable of detecting BCRP expression. However, an antibody made with a purified protein is also capable of detecting an extracellular epitope in its natural form as taught by *Nieman et al.* As cited previously, *Niman et al* (us 5,563,247) acknowledged the art-known method of using whole cell for immunization (column 3, lines 65-67), and further teach that using a polypeptide (a partial protein), even if it is synthetic, if the amino acid sequence is correspondent to the desired epitope, the produced monoclonal antibodies would react with the intact protein under a variety of reaction conditions "BECAUSE THE RECOGNITION IS LARGELY CONFORMATIONALLY INDEPENDENT", which including the condition of recognizing a *native* protein (in its natural conformation, column 16, lines 9-33, particularly line 27). Accordingly, the specification fails to teach what is now claimed because it only relies on the functional ability of an antibody to determine whether it detects a protein in its natural conformation. Therefore, in view of

the limited guidance, the lack of predictability of the art and the breadth of the claims, one skill in the art could not practice the invention without undue experimentation as it is broadly claimed.

For reasons set forth above, it appears highly unpredictable that the antibody required by the claims could be reproducibly made without undue experimentation. Although it appears that the antibody discussed in page 39 of the specification has not been reduced to practice, or evidenced to recognizes the BCRP in its natural conformation, however, if applicants provides evidence showing that the antibody was in possession of the antibody at the time the application was filed and the antibody does possess the claimed characteristics, an enabling deposit of the antibody may satisfy the requirements of 35 U.S.C. 112, first paragraph for the particular antibody.

If a deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicants, or a statement by an attorney of record over his or her signature and registration number, stating the instant invention will be irrevocably and without restriction released to the public upon the issuance of a patent, would satisfy the deposit requirement made herein. If a deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 CFR 1.801-1.809 and MPEP 2402-2411.05, Applicant may provide assurance of compliance by affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number showing that:

(a) during the pendency of the application, access to the invention will be afforded to the Commissioner upon request;

(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

(c) the deposit will be maintained in a public depository for a period of 30 years, or 5 years after the last request or for the enforceable life of the patent, whichever is longer;

(d) a test of the viability of the biological material at the time of deposit (see 37 CFR 1.807); and

(e) the deposit will be replaced if it should ever become inviable.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 16, 17, 21-28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are vague and indefinite because of the term "natural conformation". The specification fails to define the term, the meaning of the phrase is unclear in the context of the claims, and thus the metes and bounds of the claims are unclear.

The following art rejection applied even though the Examiner is aware of certain contradiction in the sections of enablement rejection and art rejection. In view of the Office policy for compact prosecution, and in view of the contradictions in the applicant's disclosure, all issues relevant will put forward in the first action on merits.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 16, 17, 21-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Ross et al* (US 6,313,277, IDS/AA), in view of *Mechetner et al* (US 5,994,088).

Ross et al teach the BCRP protein as well as the cDNA encoding such (abstract), and state, "IT IS ANOTHER OBJECTIVE OF THE INVENTION TO PROVIDE ANTIBODIES TO THE BCRP" (column 2, line 30). *Ross et al* go on to teach that the monoclonal antibody could be prepared by the numerous methods known in the art, such as immunizing a mammal with a BCRP protein (paragraph bridging columns 1 & 2) or immunizing a mammal with a whole cell with the antigen of interest on its surface and subsequently producing hybridoma secreting such antibody with spleen cells of the immunized mice (as taught in reference 7 by *Kohler et al,* Eur J. Immunol 1976;6511-9) (column 4, line 50-57). *Ross et al* do not particularly teach making the antibody that recognizes the extracellular epitope in its natural conformation.

However, at the time of the instant effective filing date, *Mechaetner et al* teach a method of making antibodies that would bind to the *extracellular portion of another ABC transporter protein*, P-glycoprotein (Pgp), in its natural conformation, i.e. "SPECIFIC... FOR WILD-TYPE PGP IN A CONFORMATION ASSOCIATED WITH SUBSTRACT BINDING" (abstract, claims 1-

9). *Mechaetner et al* teach that several of such antibodies recognizing the extracellular portion of the Pgp are known in the art, such as the 4E3 mAb as taught by *Arcesi et al* that does not disrupt drug efflux, and UIC2 that inhibit Pgp-mediated drug efflux (column 4, lines 30-65 and column 6, lines 19-46), wherein they clearly teach that the UIC2 recognizes the extracellular portion of the Pgp in its biochemical conformation (natural conformation). They go on to teach that antibodies reacting to the extracellular epitopes of Pgp are more useful for diagnosis and treatment (column 3, lines 61-67). They go on to teach the method of making such antibody, i.e. transfecting balb/c 3T3 fibroblasts with a vector comprising and expressing the cDNA of Pgp (MDR1 gene), immunizing syngeneic mice with selected cells expressing high levels of Pgp, and producing hybridomas using spleen cells of the immunized mice and selecting for antibodies of interest (e.g. column 12, lines 1-37). They also teach that the method could be used for producing monoclonal or polyclonal, chimeric or humanized antibodies (column 11, lines 45-55).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to employ the method as taught by *Mechaetner et al* in making an antibody that binds to the extracellular epitope of BCRP in its natural conformation with a reasonable expectation of success. Given the methods known in the art, given the knowledge regarding the importance of the extracellular portion of an ABC transporter protein, and given the cDNA of BCRP provided by *Ross et al*, it is within the knowledge of the skilled to make a similar antibody as 4E3 or UIC2 that binds to the extracellular epitope of BCRP in its natural conformation. Thus, the claimed

invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

In the Declaration, Dr. Sarkadi indicated "as of the priority date of May 31, 2000, there was no method known in the art to reliably produce an isolated antibody that recognizes an extracellular portion of the ABC transporter BCRB in a living cell". This statement has not obviated the instant rejection because it is noted by the Office that the cited '088 Patent teach a method of making an antibody that meets claim limitation and recognizes another ABC transporter protein, similar to BCRP. The "088 patent also disclosed additional such antibodies that are available long before the instant effective filing date (i.e. 4E3, available on or before 1994), which recognizes a conformational peptide epitope located on an external region of the mdr1 P-gp (Datasheet of DAKO). Last but not the least, the instant specification contemplates the same method as disclosed in the '088 patent. Accordingly, an expectation of success is reasonable.

The Declaration also alleged that Ross teaches preparing an antibody with a purified protein, which can have a very different conformation. In response, it is noted that Ross teach using a purified BCRP as well as an activated BCRP, and referring such to reference 7, *Kohler et al,* Eur J. Immunol 1976;6511-9, which teach a method using whole cell for immunization. Evidently, Ross is aware of more than one method of making the antibodies contemplated, and *Mechaetner et al* go further to teach a method using cells expressing the ABC transporter for immunization, as contemplated in the instant specification.

Accordingly, the rejection stands.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is 571-272-0730. The examiner can normally be reached on 9:30 am - 7 p.m., Monday through Friday, except every other Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Amy Nelson** can be reached on 571-272-0804. The fax numbers for the organization where this application or proceeding is assigned are **703-872-9306**.

Any inquiry of formal matters can be directed to the patent analyst, **Dianiece Jacobs**, whose telephone number is (571) 272-0532.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is **703-308-0196**.

JANICE LI
PATENT EXAMINER

Q. Janice Li
Patent Examiner
Art Unit 1632

QJL
March 19, 2004